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(54) Title: RETINYL ESTERS OF α-HYDROXY ACIDS FOR TOPICAL IMPROVEMENT OF SKIN FUNCTION AND APPEARANCE

(57) Abstract

Esters of retinol and α-hydroxy acids are unusually effective as skin conditioners, with significant reductions in the irritation problems characteristic of retinol and α-hydroxy acids in nonesterified form.

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RETINYL ESTERS OF α-HYDROXY ACIDS FOR TOPICAL IMPROVEMENT OF SKIN FUNCTION AND APPEARANCE

BACKGROUND OF THE INVENTION

Retinol, or vitamin A alcohol, is known to have attributes that are useful in the treatment of the human epidermis, particularly in accelerating skin renewal and skin proliferation. Retinol itself is irritating to the skin, however, and its conjugated double bonds are susceptible to oxidation, both of which detract considerably from its usefulness as a skin conditioner. These problems have been reduced by esterification of the retinol to form retinyl palmitate and acetate, for example, but these esters have shown reduced biological activity relative to the nonesterified form.

Also of relevance to the present invention are α-hydroxy acids such as glycolic acid, lactic acid, α-butyric acid, and longer chain species. These acids are known to improve skin function and appearance by accelerating desquamation and promoting stratum corneum renewal. Unfortunately, these acids as well are irritating to the skin, particularly at concentrations of 5% or higher and for individuals with sensitive skin.

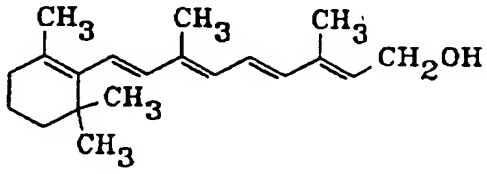
SUMMARY OF THE INVENTION

These and other problems of the prior art are addressed by the present invention, which resides in the discovery that α-hydroxy acid esters of retinol offer both a stabilized and nonirritating treatment agent, providing therapeutic and beneficial effects exceeding those of either the retinol or the α-hydroxy acids alone. By virtue of their unusually high activity and low irritancy, these esters are useful in free form, without the need to be protected by encapsulation or by liposomes. As free esters, the compounds can be incorporated into the types of formulations commonly used for topical administration to the skin, or they can diffuse into such formulations from the open pores of microscopic porous particles suspended in the formulations.

Further features, embodiments and advantages of the invention will become evident from the description that follows.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

Retinol, whose formula is shown below



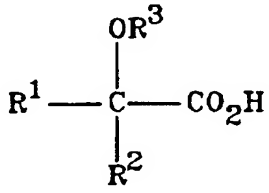
is a naturally occurring compound that can be extracted from fish liver oils in esterified form, or synthesized by methods known in the art. A synthesis from β-ionone and a propargyl halide is disclosed, for example, by Eiter *et al.*, United States Patent No. 3,060,229 (1962), and Klein *et al.*, United States Patent No. 2,972,634 (1961). The disclosures of both patents are incorporated herein by reference. A comprehensive monograph of the chemistry, physics and physiology of retinol and its provitamins is found in Sebrell, W.H., and R.S. Harris, *The Vitamins*, **Vol. I** (Academic Press, New York, 2d ed., 1967).

Many α-hydroxy acids are naturally occurring and extractable from their sources. In general, α-hydroxy acids can be synthesized by the hydrolysis of an α-halo acid or by the acid hydrolysis of the cyanohydrins of an aldehyde or ketone. Aliphatic α-hydroxy acids that do not have side chains can be prepared in good yield by the hydrolysis of α-nitrato acids with aqueous sulfite solutions, the α-nitrato acids themselves being obtainable by reacting olefins and N_2O_4 in the presence of oxygen.

The esters of this invention are readily prepared under esterification conditions well known to those of skill in the art, using a form of the α-hydroxy acid in which the α-hydroxy group is protected. Protection can be achieved by use of a cyclized diester dimer of the α-hydroxy acid, such as lactide for lactic acid. Protection can also be achieved by the use of protecting groups known to those skilled in the art of esterification. The protecting groups include those that convert the hydroxy to an ether, an ester, a carbonate, or other forms which are cleavable after the esterification reaction to return the hydroxy group to the α-position. Some of the most common examples of protecting groups are alkyl groups, benzyl groups, and silyl groups.

The esters of this invention include monoesters, but also diesters and other oligoesters. Monoesters are preferred.

The α-hydroxy acid moieties of the esters can vary widely in structure and molecular size. Preferred esters are those made from acids having the formula



in which:

R^1 is either H, C_1-C_{12} hydrocarbyl, or C_1-C_{12} hydrocarbyl substituted with one or more carboxy groups, one or more hydroxy groups, or a combination,

R^2 is either H or carboxy, and

R^3 is either H, C_2-C_{12} alkanoyl, or alpha-hydroxy C_2-C_{12} alkanoyl.

The term "hydrocarbyl" is used herein to denote any monovalent radical consisting solely of carbon and hydrogen atoms, including saturated and unsaturated groups, straight-chain and branched-chain groups. Saturated groups are preferred, and straight-chain groups are preferred. Unsaturated groups include double bonds as well as triple bonds.

The term "alkanoyl" is used herein to denote the anion R—COO^- of an ionized carboxylic acid where "R" denotes a hydrocarbyl group, preferably an alkyl (saturated hydrocarbyl) group, and most preferably a straight-chain alkyl group.

The term "carboxy" denotes the monovalent radical —COOH.

Within the scope of the α-hydroxy acids, certain subclasses are preferred. For R^1, a preferred subclass is the group H, C_1-C_8 alkyl, and C_1-C_8 alkyl substituted with one or more carboxy groups. Further preferred is the group H, C_1-C_6 alkyl, and C_1-C_6 alkyl substituted with one or two carboxy groups. For R^3, a preferred subclass is the group H, C_2-C_8 alkanoyl, and alpha-hydroxy C_2-C_8 alkanoyl. Further preferred is the group H, C_2-C_6 alkanoyl, and alpha-hydroxy C_2-C_6 alkanoyl. Specific examples of α-hydroxy acids are glycolic (*i.e.*, hydroxyacetic) acid, glyceric (*i.e.*, 2,3-dihydroxypropanoic) acid, lactic (*i.e.*, 2-hydroxypropanoic) acid, α-hydroxy octanoic acid, citric (*i.e.*, 2-hydroxy-1,2,3-propanetricarboxylic) acid, tartaric (*i.e.*, 2,3-dihydroxybutanedioic) acid, malic (*i.e.*, hydroxybutanedioic) acid, mandelic (*i.e.*, α-hydroxybenzeneacetic) acid, and O-(2-hydroxypropanoyl)lactic acid.

The esters of this invention can be applied to skin as part of a solution or an emulsion, or any other fluid form which facilitates spreading over the skin surface.

Creams and lotions with well-known formulations will be useful. These formulations typically include such ingredients as vehicles or vehicle combinations to achieve a desired viscosity or spreadability, penetration enhancers to increase absorption into the skin, emollients, antioxidants, and preservatives. When formulated in water-in-oil emulsions, for example, preferred concentrations of the esters of this invention are from about 0.3% to about 3.0% by weight of the emulsions.

Alternatively, the esters may be retained in the pores of biologically inert microscopic porous particles which can in turn be suspended in creams or lotions, or if desired, applied as a powder or incorporated into make-up and other useful products. The particles may be rigid or resiliently compressible, but in either case contain a network of interconnected pores open to the particle surface, providing substantially full communication between the internal pore space and the particle exterior. Particles of this type are disclosed by Won, in U.S. Patent No. 4,690,825; Won, U.S. Patent No. 5,145,675; Katz *et al.*, U.S. Patent No. 5,073,365; Katz *et al.*, 5,135,740; and Jankower *et al.*, U.S. Patent No. 4,873,091. The disclosures of these patents are incorporated herein by reference.

The particles are frequently spherical in shape, most often ranging from about one to about 100 microns in diameter, particularly from about 10 to about 40 microns. The pore dimensions within the particles may also vary, with optimum dimensions depending on the chemical characteristics of the polymers used to form the particles as well as the diffusive characteristics of the retinol ester retained inside. In general, best results are obtained with total pore volumes ranging from about 0.01 to about 4.0 cc/g, preferably from about 0.1 to about 2.0; surface areas ranging from about 0.1 to about 500 m^2/g, preferably from about 1 to about 400; and average pore diameters ranging from about 0.001 to about 1.0 micron, preferably from about 0.003 to about 0.3 micron.

The particles are generally organic polymers, formed by suspension polymerization, as described in the patents referenced above. Monoethylenically unsaturated monomers suitable for preparing the particles include ethylene, propylene, isobutylene, diisobutylene, styrene, ethylvinylbenzene, vinyltoluene and dicyclopentadiene; esters of acrylic and methacrylic acid, including the methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, amyl, hexyl, octyl, ethylhexyl, decyl, dodecyl, cyclohexyl, isobornyl, phenyl, benzyl, methylphenyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, propoxymethyl, propoxyethyl, ethoxyphenyl, ethoxybenzyl and ethoxycyclohexyl esters; vinyl esters, including vinyl acetate, vinyl propionate and vinyl laurate; vinyl ketones, including vinyl methyl ketone, vinylisopropyl ketone and methyl

isopropenyl ketone; and vinyl ethers, including vinyl methyl ether, vinyl ethyl ether and vinyl isobutyl ether.

Polyethylenically unsaturated crosslinking monomers suitable for use in the particles include diallyl phthalate, ethylene glycol diacrylate, ethylene glycol dimethacrylate, trimethylolpropanetrimethacrylate and divinylsulfone; polyvinyl and polyallyl ethers of ethylene glycol, of pentaerythritol, of diethyleneglycol and of resorcinol, divinylketone, divinylsulfide, allyl acrylate, diallyl maleate, diallyl fumarate, diallyl succinate, diallyl adipate, diallyl sebacate, divinyl sebacate, diallyl tartrate, and diallyl silicate.

Particularly preferred particles for use in the present invention are those formed by the copolymerization of styrene and divinylbenzene, vinyl stearate and divinylbenzene, or methylmethacrylate and ethylene glycol dimethacrylate. Usually, the monoethylenically unsaturated monomer will be present at from about 20% to about 80% of the monomer mixture, with the polyethylenically unsaturated monomer forming the remainder of the mixture.

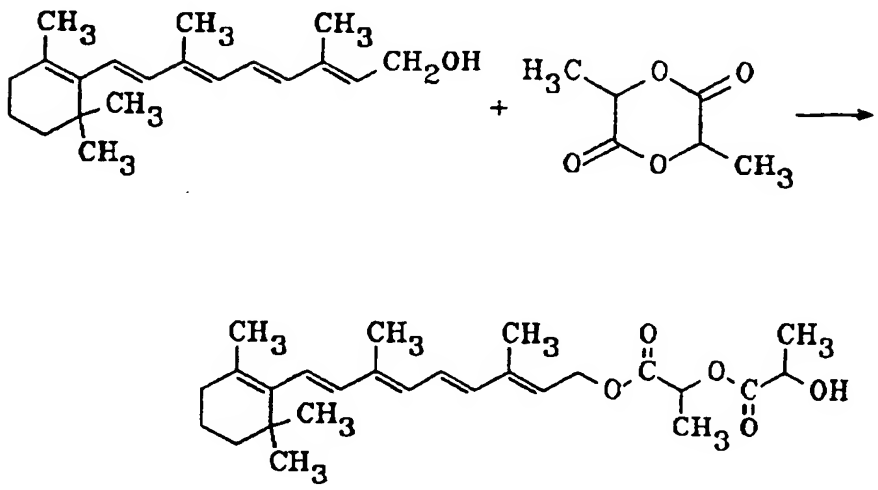
Resilient and compressible, as opposed to rigid, particles can be made by the use of curable elastomers. Examples of such elastomers are isoprene rubbers, butadiene rubbers, chloroprene rubbers, isobutylene-isoprene rubbers, nitrile-butadiene rubbers, styrene-butadiene rubbers, and ethylene-propylene-diene terpolymers.

When particles of any of the types described above are suspended in creams or lotions, the concentration of the esters of this invention relative to the entire formulation is preferably from about 0.3% to about 10.0% by weight, and most preferably from about 2% to about 5%.

The following examples are offered for illustrative purposes only.

EXAMPLE 1

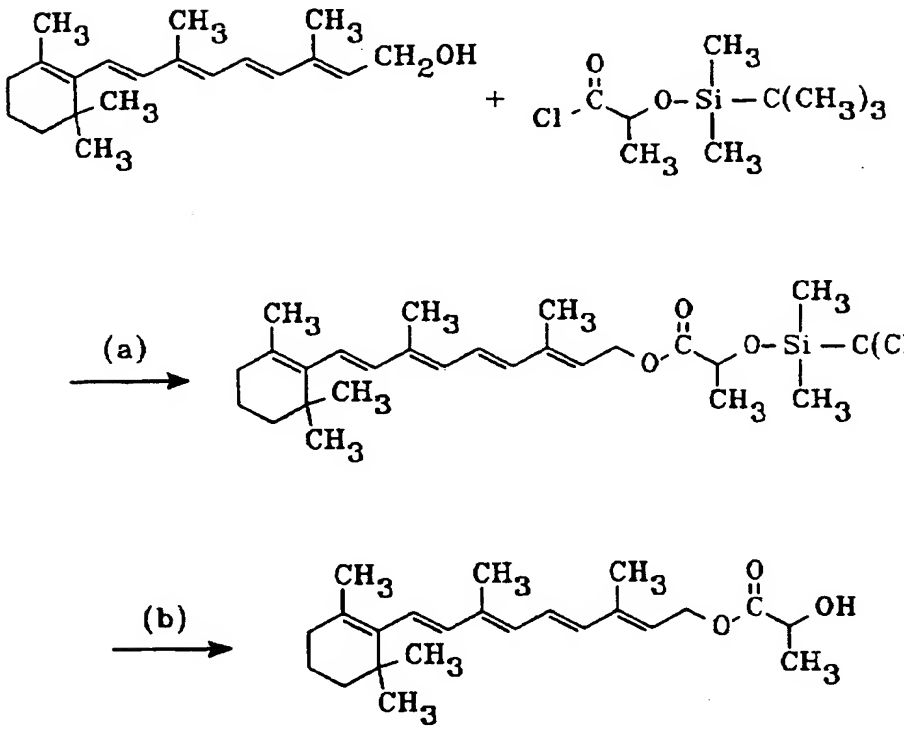
Synthesis of Ester of Retinol and O-(2-Hydroxypropanoyl)lactic Acid



Retinol (1.42 g, 5 mmol) and L-(-)-lactide (0.72 g, 5 mmol) were weighted into a screw cap tube. The tube was tightly capped, then heated in an oil bath at 120°C for one hour. Column chromatography of the crude product using silica gel and methylene chloride yielded a soft solid weighing 0.6 g. Analysis by nuclear magnetic resonance (NMR) gave a spectrum that was consistent with the retinyl ester of O-(2-hydroxy-propanoyl)lactic acid according to structure shown above.

EXAMPLE 2

Synthesis of Ester of Retinol and Lactic Acid



The following is a procedure which can be used for the reactions shown above.

To prepare the acid chloride used as a starting material in the first reaction, lactic acid was treated with 2.5 equivalents of *t*-butyldimethylsilyl chloride and 5 equivalents of imidazole in dimethyl formamide at 35°C for twenty hours to give the *t*-butyldimethylsilyl ester of *t*-butyldimethylsilyl ether of lactic acid. This compound was treated with acetic acid in tetrahydrofuran and water (volume ratios 8:8:1) to give the *t*-butyldimethylsilyl ether. The latter was then treated with $SOCl_2$ to convert the acid to the acid chloride shown.

(a) Retinol (1,42 g, 5 mmol), the *t*-butyl dimethylsilyl ether of lactyl chloride (1.12 g, 5 mmol) and pyridine (0.5 g, 6.3 mmol) were dissolved in chloroform (20 mL). The solution was stirred at room temperature under nitrogen for two hours. The solution was then washed with 0.1 N HCl, followed by dilute aqueous sodium carbonate solution. The organic solution was then dried over anhydrous $MgSO_4$ and the chloroform evaporated to leave a dry residue.

(b) The residue from part (a) was dissolved in tetrahydrofuran, and tetrabutyl ammonium fluoride solution (1.0 M in tetrahydrofuran, 10 mL, 10 mmol) was added. The resulting solution was stirred at room temperature for thirty minutes. The solution was then washed with water, dried over anhydrous $MgSO_4$ and evaporated to dryness. The product was purified by silica gel column chromatography.

While the invention is not limited to any single formulation or method of administration, two specific formulations are presented below as examples, each using porous particles of the above description, marketed by Advanced Polymer Systems, Redwood City, California, under the trade name MICROSPONGE® polymers, which are particles of methyl methacrylate/ethyleneglycol dimethacrylate approximately 18 microns in diameter, with a porosity of approximately 0.8 cc/g.

A. Anti-Aging Moisture Replenishing Cream

Part I:	Cetyl alcohol	5.0% by weight
	Myristyl myristate	5.0%
	Isopropyl myristate	4.0%
	Lanolin alcohol	0.4%
	Dimethicone	1.0%
Part II:	Retinyl lactate 30% in MICROSPONGE® polymer	10.0%
Part III:	Stearamidopropyl PG-dimonium chloride phosphate	3.0%
	GERMABEN® II (preservative) (diazolydinyl urea blends, Sutton Laboratories, Inc., Chatham, New Jersey, USA	0.2%
	Water	(balance to 100%)

Procedure:

Part III is heated to about 60°C and mixed until uniform. Part I is heated separately to the same temperature, then mixed until uniform and held at that temperature. Part III is allowed to cool to about 40°C, and Part II is added with gentle agitation. The resulting mixture is mixed until thoroughly dispersed. Part I is then added with stirring to form the emulsion. The mixture is allowed to cool to about 40°C. Fragrance and/or color are added as desired.

B. Anti-Aging Lotion

Part I:	DOW CORNING® 200 fluid (350cSt) (silicone compound, Dow Corning Corp., Midland Michigan, USA)	0.55% by weight
	Cholesterol	1.00%
	Palmitic acid	1.00%
	Stearic acid	3.00%
	Sodium palmitate	1.00%
	Mineral oil	9.70%
	Sesame oil	4.50%
	Glyceryl monostearate	2.00%
	Propylparaben	0.10%
Part II:	Retinyl glycolate 30% in MICROSPONGE® polymer	10.0%
Part III:	Propylene glycol	4.00%
	Methylparaben	0.20%
	Triethanolamine	0.50%
	Water	(balance to 100%)

Procedure:

Part III is heated to about 60°C and mixed until uniform. Part I is heated separately to the same temperature, then mixed until uniform and held at that temperature. Part III is allowed to cool to about 40°C, and Part II is added with gentle agitation. The resulting mixture is mixed until thoroughly dispersed. Part I is then added

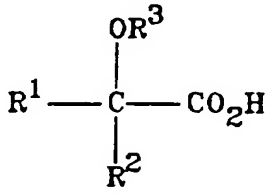
with stirring. The mixture is allowed to cool to about 40°C. Fragrance and/or color are added as desired.

The foregoing is offered primarily for purposes of illustration. It will be readily apparent to those skilled in the art that the components, proportions, formulating ingredients, methods of formulation, and methods of administration described herein may be further modified or substituted in various ways without departing from the spirit and scope of the invention.

CLAIMS:

1. An α-hydroxy acid ester of retinol.

2. An α-hydroxy acid ester in accordance with claim 1, formed from an α-hydroxy acid having the formula



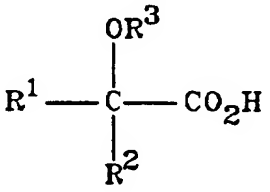
in which:

R^1 is a member selected from the group consisting of H, C_1-C_{12} hydrocarbyl, and C_1-C_{12} hydrocarbyl substituted with one or more members selected from the group consisting of carboxy and hydroxy,

R^2 is a member selected from the group consisting of H and carboxy, and

R^3 is a member selected from the group consisting of H, C_2-C_{12} alkanoyl, and α-hydroxy C_2-C_{12} alkanoyl.

3. An α-hydroxy acid ester in accordance with claim 1 in which said ester is a monoester formed from an α-hydroxy acid having the formula



in which:

R^1 is a member selected from the group consisting of H, C_1-C_{12} hydrocarbyl, and C_1-C_{12} hydrocarbyl substituted with one or more members selected from the group consisting of carboxy and hydroxy,

R^2 is a member selected from the group consisting of H and carboxy, and

R^3 is a member selected from the group consisting of H, C_2-C_{12} alkanoyl, and α-hydroxy C_2-C_{12} alkanoyl.

4. An α-hydroxy acid ester in accordance with claim 3 in which:

R^1 is a member selected from the group consisting of H, C_1-C_8 alkyl, and C_1-C_8 alkyl substituted with one or more carboxy groups,

R^2 is a member selected from the group consisting of H and carboxy, and

R^3 is a member selected from the group consisting of H, C_2-C_8 alkanoyl, and α-hydroxy C_2-C_8 alkanoyl.

5. An α-hydroxy acid ester in accordance with claim 3 in which:

R^1 is a member selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 alkyl substituted with one or two carboxy groups,

R^2 is H, and

R^3 is a member selected from the group consisting of H, C_2-C_6 alkanoyl, and α-hydroxy C_2-C_6 alkanoyl.

6. An α-hydroxy acid ester in accordance with claim 3 in which:

R^1 is a member selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 alkyl substituted with one or two carboxy groups,

R^2 is carboxy, and

R^3 is a member selected from the group consisting of H, C_2-C_6 alkanoyl, and α-hydroxy C_2-C_6 alkanoyl.

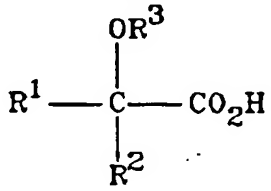
7. An α-hydroxy acid ester in accordance with claim 1, formed from an α-hydroxy acid selected from the group consisting of glycolic acid, lactic acid, α-hydroxy octanoic acid, citric acid, malic acid, and O-(2-hydroxypropanoyl)lactic acid.

8. A pharmaceutical composition for topical application, comprising:

an α-hydroxy acid ester of retinol, in a form free of encapsulation or liposomes, and

a pharmaceutically acceptable carrier tolerable to human skin.

9. A pharmaceutical composition in accordance with claim 8 in which said ester is an ester of an α-hydroxy acid having the formula



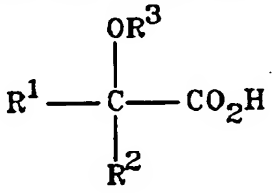
in which:

R^1 is a member selected from the group consisting of H, C_1-C_{12} hydrocarbyl, and C_1-C_{12} hydrocarbyl substituted with one or more members selected from the group consisting of carboxy and hydroxy,

R^2 is a member selected from the group consisting of H and carboxy, and

R^3 is a member selected from the group consisting of H, C_2-C_{12} alkanoyl, and α-hydroxy C_2-C_{12} alkanoyl.

10. A pharmaceutical composition in accordance with claim **8** in which said ester is a monoester of an α-hydroxy acid having the formula



in which:

R^1 is a member selected from the group consisting of H, C_1-C_{12} hydrocarbyl, and C_1-C_{12} hydrocarbyl substituted with one or more members selected from the group consisting of carboxy and hydroxy,

R^2 is a member selected from the group consisting of H and carboxy, and

R^3 is a member selected from the group consisting of H, C_2-C_{12} alkanoyl, and α-hydroxy C_2-C_{12} alkanoyl.

11. A pharmaceutical composition in accordance with claim **10** in which:

R^1 is a member selected from the group consisting of H, C_1-C_8 alkyl, and C_1-C_8 alkyl substituted with one or more carboxy groups,

R^2 is a member selected from the group consisting of H and carboxy, and

R^3 is a member selected from the group consisting of H, C_2-C_8 alkanoyl, and α-hydroxy C_2-C_8 alkanoyl.

12. A pharmaceutical composition in accordance with claim **10** in which:

R^1 is a member selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 alkyl substituted with one or two carboxy groups,

R^2 is H, and

R^3 is a member selected from the group consisting of H, C_2-C_6 alkanoyl, and α-hydroxy C_2-C_6 alkanoyl.

13. A pharmaceutical composition in accordance with claim 10 in which:

R^1 is a member selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 alkyl substituted with one or two carboxy groups,

R^2 is carboxy, and

R^3 is a member selected from the group consisting of H, C_2-C_6 alkanoyl, and α-hydroxy C_2-C_6 alkanoyl.

14. A pharmaceutical composition in accordance with claim 8 in which said ester is an ester of an α-hydroxy acid selected from the group consisting of glycolic acid, lactic acid, α-hydroxy octanoic acid, citric acid, malic acid, and O-(2-hydroxypropanoyl)-lactic acid.

15. A pharmaceutical composition in accordance with claim 8 in which said pharmaceutically acceptable carrier is comprised of solid porous particles with said α-hydroxy acid ester retained in pores thereof.

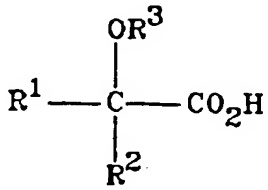
16. A pharmaceutical composition in accordance with claim 15 in which said pharmaceutically acceptable carrier is comprised of said solid porous particles dispersed in a fluid selected from the group consisting of creams and lotions.

17. A method of treating human skin comprising applying topically to said skin a pharmaceutical composition for topical application, comprising:

an α-hydroxy acid ester of retinol, in a form free of encapsulation or liposomes, and

a pharmaceutically acceptable carrier tolerable to human skin.

18. A method in accordance with claim 17 in which said ester is an ester of an α-hydroxy acid having the formula



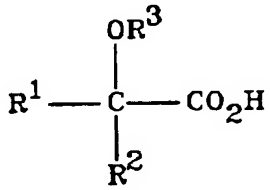
in which:

R^1 is a member selected from the group consisting of H, C_1-C_{12} hydrocarbyl, and C_1-C_{12} hydrocarbyl substituted with one or more members selected from the group consisting of carboxy and hydroxy,

R^2 is a member selected from the group consisting of H and carboxy, and

R^3 is a member selected from the group consisting of H, C_2-C_{12} alkanoyl, and α-hydroxy C_2-C_{12} alkanoyl.

19. A method in accordance with claim **17** in which said ester is a monoester of an α-hydroxy acid having the formula



in which:

R^1 is a member selected from the group consisting of H, C_1-C_{12} hydrocarbyl, and C_1-C_{12} hydrocarbyl substituted with one or more members selected from the group consisting of carboxy and hydroxy,

R^2 is a member selected from the group consisting of H and carboxy, and

R^3 is a member selected from the group consisting of H, C_2-C_{12} alkanoyl, and α-hydroxy C_2-C_{12} alkanoyl.

20. A method in accordance with claim **19** in which:

R^1 is a member selected from the group consisting of H, C_1-C_8 alkyl, and C_1-C_8 alkyl substituted with one or more carboxy groups,

R^2 is a member selected from the group consisting of H and carboxy, and

R^3 is a member selected from the group consisting of H, C_2-C_8 alkanoyl, and α-hydroxy C_2-C_8 alkanoyl.

21. A method in accordance with claim **19** in which:

R^1 is a member selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 alkyl substituted with one or two carboxy groups,

R^2 is H, and

R^3 is a member selected from the group consisting of H, C_2-C_6 alkanoyl, and α-hydroxy C_2-C_6 alkanoyl.

22. A method in accordance with claim 19 in which:

R^1 is a member selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 alkyl substituted with one or two carboxy groups,

R^2 is carboxy, and

R^3 is a member selected from the group consisting of H, C_2-C_6 alkanoyl, and α-hydroxy C_2-C_6 alkanoyl.

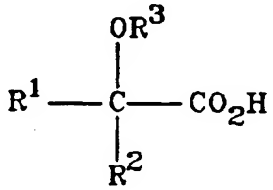
23. A method in accordance with claim 17 in which said ester is an ester of an α-hydroxy acid selected from the group consisting of glycolic acid, lactic acid, α-hydroxy octanoic acid, citric acid, malic acid, and O-(2-hydroxypropanoyl)lactic acid.

24. A method in accordance with claim 17 in which said pharmaceutically acceptable carrier is comprised of solid porous particles with said α-hydroxy acid ester retained in pores thereof.

25. A method in accordance with claim 24 in which said pharmaceutically acceptable carrier is comprised of said solid porous particles dispersed in a fluid selected from the group consisting of creams and lotions.

26. The use of an α-hydroxy acid ester of retinol for the manufacture of a medicament for treating human skin.

27. The use of claim 26 in which said ester is an ester of an α-hydroxy acid having the formula



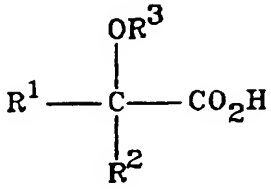
in which:

R^1 is a member selected from the group consisting of H, C_1-C_{12} hydrocarbyl, and C_1-C_{12} hydrocarbyl substituted with one or more members selected from the group consisting of carboxy and hydroxy,

R^2 is a member selected from the group consisting of H and carboxy, and

R^3 is a member selected from the group consisting of H, C_2-C_{12} alkanoyl, and α-hydroxy C_2-C_{12} alkanoyl.

28. The use of claim 26 in which said ester is a monoester of an α-hydroxy acid having the formula



in which:

R^1 is a member selected from the group consisting of H, C_1-C_{12} hydrocarbyl, and C_1-C_{12} hydrocarbyl substituted with one or more members selected from the group consisting of carboxy and hydroxy,

R^2 is a member selected from the group consisting of H and carboxy, and

R^3 is a member selected from the group consisting of H, C_2-C_{12} alkanoyl, and α-hydroxy C_2-C_{12} alkanoyl.

29. The use of claim 28 in which:

R^1 is a member selected from the group consisting of H, C_1-C_8 alkyl, and C_1-C_8 alkyl substituted with one or more carboxy groups,

R^2 is a member selected from the group consisting of H and carboxy, and

R^3 is a member selected from the group consisting of H, C_2-C_8 alkanoyl, and α-hydroxy C_2-C_8 alkanoyl.

30. The use of claim 28 in which:

R^1 is a member selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 alkyl substituted with one or two carboxy groups,

R^2 is H, and

R^3 is a member selected from the group consisting of H, C_2-C_6 alkanoyl, and α-hydroxy C_2-C_6 alkanoyl.

31. The use of claim 28 in which:

R^1 is a member selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 alkyl substituted with one or two carboxy groups,

R^2 is carboxy, and

R^3 is a member selected from the group consisting of H, C_2-C_6 alkanoyl, and α-hydroxy C_2-C_6 alkanoyl.

32. The use of claim 26 in which said ester is an ester of an α-hydroxy acid selected from the group consisting of glycolic acid, lactic acid, α-hydroxy octanoic acid, citric acid, malic acid, and O-(2-hydroxypropanoyl)lactic acid.

INTERNATIONAL SEARCH REPORT

Int al Application No
PCT/US 96/19580

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C403/12 A61K7/48 A61K31/07 A61K31/215

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 16659 A (AVON PROD INC) 22 June 1995 see the whole document ---	1-32
A	DE 44 15 204 A (WEISCHER CARL HEINRICH DR) 2 November 1995 see claims -----	1,8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
14 March 1997	26.03.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Bonnevalle, E

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 96/19580

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17-25 are directed to a method of treatment of the human body the search has been carried out and based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

...formation on patent family members

In ...al Application No
PCT/US 96/19580

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9516659 A	22-06-95	AU 8052094 A	03-07-95
		CA 2178964 A	22-06-95
		EP 0734371 A	02-10-96
		US 5605933 A	25-02-97
DE 4415204 A	02-11-95	NONE	